

REMARKS

Claims 1-10, 12-52, 55-64, 69 and 67-72 are cancelled and claim 11 has been amended without prejudice to, or disclaimer of, the subject matter therein. Applicants reserve the right to pursue the cancelled subject matter by way of continuing or divisional applications. New claims 73 and 74 have been added. Support for the new and amended claims may be found in the original claims and throughout the specification. Thus, no new matter has been added.

Claims 11, 53, 54, 65, and 66 are pending in the current application.

The rejection of claims 65 & 66 under § 112 should be withdrawn

Written Description. Claims 65 and 66 stand rejected under § 112, written description. Applicants respectfully disagree.

The rejection alleges that "...the specification does not teach the protective immunoepitope(s) of a SEQ ID NO:34 so that one of skill in the art can envision which regions of the amino acid can be conservatively substituted and still retain immunogenicity and protectiveness." This statement is factually incorrect: Applicants have already drawn the Office's attention to such guidance within the specification, namely the predicted epitopes of SEQ ID NO:34 on page 99, Table 5 and Table 6. See the Response filed 7 Oct 2009, p. 10, first full paragraph.

Further, at the time of filing, the BrkA polypeptide had already been described in the scientific literature; much was known about its structure, including its sequence and structural regions. See the Response filed 7 Oct 2009, p. 10, second full paragraph. Given the knowledge in the art of the structure of BrkA, including which portions are located on the surface and which are embedded in the membrane, as well as the guidance provided within the specification, there is substantial evidence in the record to support a conclusion that the skilled person would have recognized that Applicants were in possession of the claimed subject matter as amended.

Given this evidence, Applicants suggested that Example 11 of the 2008 Written Description Training Materials should be followed. Example 11 deals with a hypothetical situation in which there is an art-recognized structure-function correlation present, as here, and concludes that written description is satisfied for

sequences of at least 85% identity to a disclosed species (the same degree of identity recited in Applicants' claims).

Instead of explaining the deviation from the Guidelines, the rejection relies on Greenspan (1999) *Nature Biotechnology* 7:936-937. Greenspan is not pertinent to the present inquiry for two reasons. First, Greenspan deals with the inconsistencies between two methods for structurally defining the *specific amino acids* involved in non-covalent interactions at epitope binding sites, irrelevant here because an epitopic region of a protein can be predicted without defining which specific amino acids non-covalently interact. Second, the rejection fails to explain why the skilled person would consider substituting *any* of the amino acids within the predicted epitopes given the guidance in Tables 5 and 6.

Given the incorrect factual finding regarding the guidance within the specification, the deviation from Example 11 of the Guidelines, and the weight of the evidence favoring a conclusion that the claimed subject matter satisfies the written description requirement, the rejection of claims 65-66 for allegedly lacking written description should be withdrawn.

Enablement. Claims 65 and 66 stand rejected under § 112, enablement. Applicants respectfully disagree.

The rejection states that the claims are not enabled because they encompass "all vaccines to an unnamed pathogen...." This point cannot support an enablement rejection: There is no legal requirement that a composition claim must recite any use for the composition claimed.

The rejection repeats the allegation from the written description rejection that "...the specification does not teach the protective immunopitope(s) of a SEQ ID NO:34...." This is factually incorrect given the guidance of Tables 5 and 6, as discussed elsewhere herein.

The rejection also alleges that Examples 12 and 13 do not demonstrate that the claimed "...composition confers 'protection' against any type of infection. It merely shows that said composition reduces infection." This reasoning is flawed for at least three reasons:

- First, the logic utilized in the rejection leads to a factually unsupportable conclusion. The cellular pertussis vaccine, DTPw, was used as a control in

the murine model discussed in Examples 12 and 13. In Example 13, DTPw protection was statistically equivalent to protection conferred by the experimental pertussis toxin/FHA/BrkA-containing composition. If the reasoning regarding the experimental composition was correct, then the same reasoning must apply to the cellular pertussis vaccine (both conferred statistically equivalent protection). This leads to the factually unsupportable conclusion that the time-tested cellular pertussis vaccine does not confer protection against *pertussis* challenge in mice.

- Second, the rejection takes the position immunogenic compositions that reduce pertussis infection do not necessarily confer protection. This is incorrect. As stated in the specification at paragraph 5, "It is widely acknowledged that current vaccines protect against severe disease but do not eliminate *Bordetella pertussis* from the body (Cherry et al (1998) Vaccine 16:1901; Hewlett and Halperin (1998) Vaccine 16:18999; Storsaeter (1998) Vaccine 16:1907." This supports a conclusion that the term "protection" would be understood by the skilled person to encompass reducing the severity of a pertussis-caused disease.
- Third, the allegation that data obtained from a mouse model fails to correlate with protection is factually and scientifically flawed. Applicants utilized a respiratory challenge lung-clearance model in mice to assess protection conferred by the various compositions tested in Examples 10-13. Mouse respiratory challenge models are scientifically accepted models for pertussis vaccine efficacy. See, e.g., Mills (1998) "A Murine Model in Which Protection Correlates with Pertussis Vaccine Efficacy in Children Reveals Complementary Roles for Humoral and Cell-Mediated Immunity in Protection against *Bordetella pertussis*," *Infection and Immunity*, 66:594-602 (made of record by IDS filed contemporaneously herewith).

These factual and legal errors are repeated throughout the findings made in support of the rejection. Given these errors, the rejection should be withdrawn.

The rejection also relies on Bowie (1990) *Science* 247:1306-1310 for the premise that changes to a protein's amino acid sequence that "...can be made with a reasonable expectation of maintaining function are limited." Applicants' representative has carefully reviewed Bowie and cannot determine where it provides

any teaching regarding the immunogenicity of a protein. Rather, the reference seems to relate to changes to a protein's amino acid sequence that would maintain the native protein function. Clarification is requested.

It is elemental that a rejection founded on factual or legal error cannot be maintained. Given the factual and legal errors, the rejection of claims 65-66 for allegedly lacking enablement must be withdrawn.

The rejection of claims 11, 53, and 54 under § 103 should be withdrawn

Pending claims 11, 53, and 54 stand rejected over the combination of Novotny, Oliver, and Petermans in view of Kinnear and Pagliaccia. (Claims 29 and 32 have been canceled and their rejection mooted.)

The Examiner reasons that "Novotny teach an acellular pertussis vaccine comprising a combination of *Bordetella pertussis* antigens, wherein said combination consist of isolated and purified 69 kDa antigen ... and isolated and purified ... FHA..., wherein the 69 kDa antigen (**pertussis toxin**) and the [FHA] are present in a ratio...." See the Office Action mailed 2 Mar 2010 (O.A.), paragraph spanning page 13-14 (emphasis added). After discussing Oliver and Peetermans, the rejection concludes that "...it would have been obvious to use SEQ ID NO:34, FHA, pertussis toxin, and pertactin because these antigens are taught to be useful for that purpose."

To reject a claim based on the rationale that a claimed invention is a combination of prior art elements according to known methods to yield predictable results, the Examiner must at least articulate the following: (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference; (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately; (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. MPEP 2142. In addition, it must be established that the skilled person would have a reasonable expectation of success. MPEP 2143.02.

Factual and legal errors in these findings are one basis on which a rejection can be reversed.

The rejection is founded on a factual error related to Novotny. Specifically, the rejection finds that the 69 kDa antigen is pertussis toxin. From this starting point, the rejection then reasons that Novotny teaches a composition comprising pertussis toxin and FHA. It alleges that Novotny differs from the presently claimed subject matter only “in that they don’t explicitly disclose the BrkA protein (SEQ ID NO:34)....” But this reasoning is founded on a factual error, as described in the next paragraph.

The 69 kDa antigen of Novotny **is not** pertussis toxin, it is ***pertactin***. Novotny actually teaches that the combination of ***pertactin*** (the 69 kDa antigen) and FHA is synergistic. See Novotny, col. 3, lines 21-25: “There is also provided a synergistic combination comprising i) the 69 kDa antigen from *B. pertussis* and ii) the filamentous haemagglutinin antigen [FHA] of *B. pertussis* in an amount effective to induce protection in a mammal to subsequent challenge by a virulent strain of *B. pertussis*.” Novotny supports a conclusion that the skilled person would find that pertactin is *necessary* for a satisfactory immune response, not a conclusion that that the skilled person would reasonably expect that the presently claimed BrkA/pertussis toxin/FHA combination would be successful.

The rejection combines Novotny with Oliver. Although Oliver does teach the BrkA protein, its combination with Novotny would produce the elements of pertactin/FHA/BrkA, not the elements presently claimed. And Oliver fails to establish that the skilled person would reasonably expect that a BrkA/pertussis toxin/FHA combination would be successful.

It is actually Applicants’ own disclosure that shows that a BrkA/pertussis toxin/FHA combination can confer a level of protection that is statistically equivalent to that provided by compositions comprising pertactin or whole-cell pertussis vaccine in a scientifically accepted animal model. See Examples 12 and 13.

Applicants’ result would not have been predictable to the skilled person, as evidenced by Poolman (2007) *Expert Rev. Vaccines* 6:47-56 (considered by the Office 25 Feb 2009). Poolman discusses a limited number of efficacious *B. pertussis* proteins for use in acellular vaccine compositions. Despite being published five years *after* Oliver, Poolman does not include BrkA among the efficacious *B. pertussis* antigens. Instead, Poolman teaches that “...vaccines that contain PT

[pertussis toxin] and PRN [pertactin] are considered to be the more effective pertussis vaccines.” See Poolman, first full sentence on page 48. Poolman constitutes evidence that the person of skill in the art would not reasonably expect the presently claimed that a BrkA/pertussis toxin/FHA combination to produce the observed level of protective immunity.

In the final rejection, Peetermans was added for discussing 2- and 3-component pertussis vaccines. Peetermans also teaches combining 2- and 3-component pertussis vaccines with polio or hepatitis antigens, as well as other polysaccharide conjugate vaccines to generate a multivalent vaccine. This does not establish that the skilled person would reasonably expect a BrkA/pertussis toxin/FHA combination to be successful.

Neither Kinnear nor Pagliaccia cure the deficiencies of the other references.

By itself, the factual error regarding Novotny forecloses the establishment of a prima facie case under § 103. Moreover, the evidence of record weighs against the rejection. For all these reasons, Applicants request the withdrawal of the rejection of claims 11, 53, and 54.

CONCLUSION

For all of the preceding reasons, the rejection of claims 11, 53, 54, 65, and 66 should be withdrawn, and should not be asserted against new claims 73 and 74. Applicants respectfully submit that the claim set as amended is in condition for allowance. Early notice to this effect is solicited.

The Commissioner is hereby authorized to charge any fees required or credit

any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

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Date: 27 Oct 2010

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